UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

October 15, 2002

MEMORANDUM

SUBJECT: EFED response to Syngenta's errors-only comments on the Agency document "Comparative Risks of Nine Rodenticides to Birds and Nontarget Mammals"

TO: John Pates, Chemical Review Manager
Susan Lewis, Branch Chief

FROM: William Erickson, Biologist
Douglas Urban, Senior Biologist
Environmental Risk Branch III, Environmental Fate and Effects Division

THRU: Stephanie Irene, Acting Chief
Environmental Risk Branch III, Environmental Fate and Effects Division

The Environmental Fate and Effects Division (EFED) has reviewed Syngenta's 30-day errors-only response to the Agency document "Comparative Risks of Nine Rodenticides to Birds and Nontarget Mammals" dated October 3, 2001. Syngenta's comments of December 5, 2001 were prepared by J. Hott, Regulatory Product Manager, with support from J. Akins, Toxicologist; D. Kaukeinen, Technical Specialist; and J. Shaw, Environmental, Stewardship and Policy Leader. As stated in the Agency's October 23, 2001 cover letter sent for the assessment, the registrants' 30-day response should address only mathematical, computational, typographic, or other similar errors. Matters of policy, interpretation, or applicability of data will be addressed after the public comment period in accordance with the Agency's reregistration process for pesticides.

In response to error comments by Syngenta, other rodenticide registrants, and the Rodenticide Registrants Task Force, EFED has made necessary computational and/or typographical corrections. However, EFED notes that many comments relate to policy, interpretation, or applicability of data, and those comments will be addressed along with public comments after the 60-day public-comment period.

"Comparative Risks of Nine Rodenticides to Birds and Nontarget Mammals":

Syngenta Response

GENERAL COMMENTS

Document is not a "Risk Assessment".
The EPA document "Comparative Risks of Nine Rodenticides to Birds and Nontarget Mammals" reviews hazard studies and incidents and develops hazard indices, but does not adequately address the important exposure portion to establish "Risk". There is a clear difference between the term and meaning of "Risk" as compared to "Hazard". Risk is a function of the Hazard (toxicity characteristics) and exposure (product use and associated exposure potential). Given that the remit of EFED biologists was to produce a Rodenticide Risk Assessment, we maintain that this goal has not yet been achieved because no exposure analysis has been provided. In fact, the resulting "Hazard Study" is preliminary to a Problem Formulation stage, which would normally precede a Risk Assessment.

> **EFED response:** This has been addressed in the revised document. As Syngenta knows, rodenticide baits are formulated to be lethal to rodents and a few other small mammals, and they are not selective to the target species. Although many factors influence which nontarget animals might be exposed to baits, many nontarget organisms are attracted to and consume grain-based baits. Predators and scavengers also feed on rats and mice or other target species, and they are not likely to avoid feeding on those that have eaten rodenticide bait. Thus, rodenticide baits also pose potential secondary risks. EFED believes that the potential for risks to birds and nontarget mammals is well established for some of these rodenticides.
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> The risk assessment is based on the available data. Registrants, including Syngenta, have not submitted the data that would be needed to assess the probability of exposure. These data have been outlined in a section on *Uncertainty and Data Needs* in the revised assessment. The methodology used is similar to that used in the Agency's "Comparative Analysis of Acute Risk From Granular Pesticides" (EPA 1992) and "A Comparative Analysis of Ecological Risks from Pesticides and Their Use: Background, Methodology, Case Study" (EPA 1998); both were reviewed by a FIFRA Scientific Review Panel. Concerning the latter analysis, the Panel noted the many scientific uncertainties in the method, yet agreed that it was a useful screening tool that provides a rough estimate of relative risk. The Panel made a number of helpful suggestions to improve the utility of the method, most of which are included here.
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> Risk conclusions are presented in tabular and graphical form based on two analyses of the available data. The first is a comparative ranking of the potential risk based on a comparative-analysis model, and the second is a tabular comparative rating of potential risk based on a qualitative "weight-of-evidence" assessment. Quantitative estimates of

risk are used in both; however, the "weight-of evidence" assessment includes qualitative assessments of secondary risk based on mortality and other adverse effects reported in laboratory and field studies, operational control programs, and incident reports, as well as toxicokinetic data and residue levels reported in primary consumers. This approach is in concert with EPA's risk-assessment guidelines (EPA 1998), where professional judgement or other qualitative evaluation techniques may be used to rank risks using categories such as low, medium, and high when exposure and effects data

Document does not provide for "Risk/Benefit" Considerations.
The benefit analysis and regulatory history sections are completely absent in the EPA Comparative Assessment document as compared with the EPA RED in 1998 (page 102-103, 7-8). This is an error based on the FIFRA law, which is a Risk-Benefit law. These are especially important sections, since the target species and non-target species (mammals) are nearly identical physiologically. It is impossible to identify a rodenticide that poses no risk to mammals, and the EPA "recognizes that new technologies do not exist" for rodent control (EPA RED Rodenticide Cluster).

In other Reregistration Eligibility Decision and Reduced Risk assessments with which we are familiar, the Agency systematically addresses the products' use in accordance with benefits, including Resistance Management. The second-generation rodenticides were designed to control populations of rodents that are resistant to the first generation rodenticides and to eliminate the need for refeeding to ingest lethal doses. The ecological risk posed by second-generation rodenticides should be analyzed separately from the first generation. First generation rodenticides should not be used to replace the second-generation rodenticides unless one is willing to further increase the range of resistant rodent populations and return to the greater exposure represented by refeeding requirements.

The benefits of rodenticides in general in combating harmful pest rodents need to be considered. Acceptable risk levels for rodenticides cannot be set without establishing some measure of the economic and public health detriments that pest rodent cause.

EFED response: The Agency will be considering benefits of rodenticides in a later phase of the reregistration process. The current document is EFED's assessment of risks.

Exposure considered comparable for all rodenticides.

The Review's assumption that exposure of non-target organisms is equivalent for the various rodenticides (pages 1-2 and elsewhere) ignores very significant differences in activity and action, market share, label uses, and formulation differences. Risks will not increase or decrease equally if one rodenticide is used instead of another. In fact, some rodenticides have singular utility. Brodifacoum, for example, is the only anticoagulant documented and labeled to control both warfarin-resistant rats and warfarin-resistant

mice. Brodifacoum can be used outside of structures in non-urban areas, whereas bromadiolone and difethialone cannot. Bromadiolone and brodifacoum can be used outside in burrows, but difethialone cannot. So there cannot be an equal substitution of one second-generation anticoagulant for another. The brodifacoum label is broader than the other products in recognition of its superior efficacy and the additional data that was provided by Syngenta and its heritage companies.

> **EFED response:** EFED's previous comment addresses exposure. EFED also notes that the Agency requested use information from registrants prior to issuance of the Rodenticide Cluster Reregistration Eligibility Document (RED), but that information was not provided. Differences is uses among the rodenticides will be considered and reevaluated during the reregistration process.

Toxicological and hazard findings taken out of context.

Rodenticides are by their nature, vertebrate pesticides. No "perfect rodenticide" has yet been developed that is specific to rodents. It is hardly surprising that non-target animals can be poisoned under controlled conditions in the laboratory or through misuse in the field. However, such findings are often irrelevant or insignificant in regard to the commercialized, intended use pattern. Yet this review presents an exhaustive summary of such disparate information as a basis for Agency concern. Likewise, a review of incident data is not a substitute for an exposure assessment. Incidents are a function of the prevalence of use and how the product is used or misused. Incident data would more properly be useful in the development of a Problem Formulation stage of a risk assessment, prior to an exposure analysis.

Highly different studies and incident situations are grouped together in this document for comparison. No consideration is given to the quality of studies, the purposes for which they were conducted, and their appropriateness for a risk evaluation. The abbreviated nature and wide data spread of many studies make their utility limited. In many cases in conclusions and calculations, specific non-target animal feeding behaviors and diet preferences are ignored in making assumptions of amounts of rodenticides consumed directly (primary exposure) or indirectly (secondary exposure). Many incidents appear to have no confirmed cause of death, or have multiple causative factors.

The use patterns and practices that have been developed and formalized into labeling statements and the products allowed by the Agency to be marketed have resulted from extensive studies that registrants have conducted to meet Agency requirements. The efficacy studies required for the advanced anticoagulants (single-feed) in particular have selected for highly active products. It now seems the Agency is concerned about the very product qualities that directly resulted from the very test requirements that registrants were required to meet from the EPA. Evaluations with compounds such as brodifacoum have been extensive.

Advanced non-target risk evaluations involving radio telemetry studies were conducted at the request of the Agency under an EUP program, in full consultation with Agency biologists. The resulting barn owl field study evaluated commensal rodent baiting hazards for brodifacoum to the raptor most at risk, and the Agency accepted both the protocol for this work as well the independent study directors' findings (Hegdal and Blaskiewicz, 1984). These findings were that commensal baiting did not pose a significant risk to populations of barn owls. Too little has been made of this study in the Agency "Comparative Risk" document which, at its core, is about raptor hazard with an emphasis on brodifacoum. In fact, the barn owl study met the Tier 3 requirements that addressed these non-target concerns back in the early 1980s. It is entirely proper to question older data, but no information is presented to refute the earlier findings, and they should not be ignored. The barn owl findings resulted in the Agency allowing brodifacoum products to be used outside of structures in non-urban areas, unlike the other advanced anticoagulants.

Furthermore, the EPA stated in the 1998 RED that:
"The U. S. Environmental Protection Agency (EPA) has completed its reregistration eligibility decision of the pesticides brodifacoum, bromadiolone, chlorophacinone, diphacinone and its sodium salt, bromethalin, and pival and its sodium salt. This decision includes a comprehensive reassessment of the required target data and the use patterns of currently registered products. These chemicals are rodenticides used in urban, suburban, and rural areas for the control of commensal rodents. …. With the exception of pival and its sodium salt, the Agency has concluded that the uses, as prescribed in this document, with additional labeling requirements and a number of risk mitigation measures, will not cause unreasonable risks to humans or the environment…The Agency has determined that all uses of brodifacoum, bromethalin, and bromadiolone are eligible for reregistration."

> **EFED response:** This is not an errors response. These issues will be addressed along with other responses after the public-comment period.

Pooling of Wildlife Incident Data.

In other Reregistration Eligibility Decision and Reduced Risk assessments that have been addressed by the Agency over the last ten years or more, the Agency systematically addresses the product's use and resulting exposure and risk potential to nontarget wildlife. The current document mentions the use site areas, but it does not separate the uses regarding risk. Three critical issues, pertaining to incident data, that need to be addressed are listed below:

1) The EPA over-interprets the impacts of residue analysis to the causation of mortality. Low levels of persistent compounds such as brodifacoum cannot be directly related to cause of death, particularly when case study information indicate other lethal or potentially lethal effects such as vehicle impact. The Agency should break out

incident data where causation cannot be determined or where multiple potential causative factors were identified.

2) When comparing the incident or study data between active ingredients, the EPA should take into account how and where the product was used, and the total amount of product that is being used. In order to allow for comparisons to be made, the Agency should, at a minimum, divide incidents into the following groups:

a) Incident occurred by intentional poisoning;

b) Incident resulting from the experimental application of a rodenticide (e.g., for control of orchard voles) in efficacy or hazard studies involving a use pattern that is different from the commensal rodent use pattern.

c) Incident occurred by off-label use in the United States (e.g., misapplications or uses in other countries that are different that US);

d) Incident occurred by currently labeled use.

3) Establish the total sales of the product compared to the total number of incidents.

i) It is important to take into account the total sales of a product and use of a product before comparing risk. In the case of brodifacoum, the Agency indicates that the product has 180 incidents, which the Agency alleges is far more than the other rodenticides. However, earlier in the document, the Agency states that brodifacoum makes up for more than 93% of the total sales of rodenticides in the United Sates. When the ratio of incidents to containers sold for brodifacoum in 1997 is compared with four other rodenticides incidents to sales ratio in 1997, brodifacoum is determined to pose the least risk (Table 1). Based on this analysis, if bromodiolone were to replace brodifacoum, one would expect a 31-fold increase in wildlife incidents with bromodiolone.

ii) This analysis should be conducted once the above steps are completed to take into account the product use and confidence in the causation.

Table 1. Incident Risk Based on Total Product Sold.

Rodenticide	Total incident # *	Total incident # in 1997	Total Container Sales in 1997	# Incidents / Total Containers Sales in 1997	# Incidents in 1997/ Total Container Sales in 1997***
Brodifacoum	180	**	44,144,456	0.0000041	<< 0.0000041
Bromadiolone	37	**	294,706	0.00013	< 0.00013
Diphacinone	18	**	2,860,419	0.0000063	<< 0.0000063
Chlorophacinone	10	**	18,360	0.00054	< 0.00054

* The number of incidents is captured from many years.
** This number needs to be calculated.
*** This number needs to be calculated taking into account the total number of containers sold over the same period of time that the incidents were recorded.

EFED response: EFED believes it is highly misleading to refer to "total" incidents, rather than "reported" incidents, because most incidents are not reported. The Agency does not know the amount of brodifacoum or other rodenticides sold and applied in the U. S., although we have repeatedly requested this information from rodenticide registrants. The statement that brodifacoum accounts for 93% of the over-the-counter sales (not total sales) was attributed to an RRTF article (Kaukeinen et al. 2000) in a conference proceedings. However, the only information provided is container sales for four of the nine rodenticides. No information is provided regarding container sizes, regional or state use, or other important use information.

In a meeting with the Agency on October 9, 2002, the RRTF provided a handout on "Estimates of % Chance of Incidents Occurring Based on Total Number of OTC Placements". The chance of an incident occurring was based solely on an estimate of total placements compared to the total number of incidents reported. However, such estimates are of little value without factoring in the probability that an incident occurs but is not discovered, the probability that an incident is discovered but not reported to the proper authorities, and the probability that an incident is reported but no residue analysis is conducted. Moreover, simply considering over-the-counter sales completely ignores incidents that might occur from use by Certified Applicators.

Statistical Methodology

The EFED has not utilized standard and conventional methodologies that allow for a true risk assessment on rodenticidal baits and thus, this document falls short of the standard EFED Tier 1 Agency assessments that we are familiar with for other products. No scientific rationale is provided to support the methodology and approach used by EFED. The HD5 method, for example, is utilized in the document for rodenticides; will all

pesticides now be analyzed by the HD5 method? Is this method recommended by the EFED Probabilistic Risk Assessment team as more appropriate than other methods? Summary values produced by the analyses do not provide a comparison of risk, but rather reflect the particular 'measures of effect' selected by EFED and the weighing that EFED gave them. Parameters such as body retention times are only one component and do not necessarily relate to risk determination.

A decision-making analysis does not appear to be appropriate for an ecological risk assessment, nor is it an adequate substitute for the scientific evaluation of exposure and risk. Such a decision-making analysis might more properly be used following completion of a risk assessment, such as in a 'reduced risk rationale'.
Based upon our exposure to the science of risk assessment, we believe there are better and more appropriate approaches to develop probabilistic methods with better application to rodenticides than those chosen by EFED in this review.

> **EFED response:** This is not an errors response, but EFED notes that EFED's Probabilistic Risk Assessment team and Division Director were consulted. They, as well as numerous internal and external reviewers, concurred that the approach used in the assessment is appropriate for the available data. See also previous comments.

Specific Errors and Comments:

The references to 2-gram pellets (pages 45, 46, 57 and 91) are incorrect. Talon pellets of 3/16 inch weigh, on average, 0.2 grams each, not 2 grams. Therefore, an animal eating 2 grams of Talon would need to be ingesting 10 pellets, not one. Only for mice or mouse-sized animals does an LD50 allow for one brodifacoum pellet to approximate a lethal dose. Likewise, calculations such as in Table 31 equating LD50 to dose in numbers of pellets are off by an order of magnitude because of this error.

> **EFED response:** The size of the bait pellet has been corrected in the revised assessment.

The "Bird LD50" (page i and elsewhere) of 0.26 mg/kg is actually the mallard LD50. Other birds including raptors have LD50s of 10 to 40 times this amount (Godfrey, 1985). It is misleading to choose the lowest LD50 figure to represent all bird species. The mallard study utilized a vitamin K-deficient diet, causing an abnormally low value; a normal diet produced a mallard LD50 of 2.0 mg/kg.

> **EFED response:** EFED reports an LD50 of 0.26 mg/kg for the mallard in Table 3 of the risk assessment. That value is based on a "core" study submitted to the Agency. Syngenta has provided no documentation that the mallard acute-oral study was based on a vitamin K-deficient diet. In fact, a previous acute oral study was invalidated because vitamin K (an antidote) had been added to the test diet. The value of 2.0 mg/kg cited by Syngenta is actually an LC50 from a dietary study, and it is reported as an LC50 value in Table 3 and is used in the RQ calculations for dietary risk. Syngenta should also note

that Table 3 lists LD50 values of <0.75 mg/kg for both the Canada goose and the southern black-backed gull, neither of which is "10 to 40 times" greater than the value of the mallard.

It is inappropriate to group end-point results of different toxicology studies from the standpoint of risk assessment (pages i, ii, 19, 151 and elsewhere). Many of these studies were designed to reach an endpoint. The greater number of studies on brodifacoum are a result of its popularity as a rodenticide. Fewer studies were done on other anticoagulants so fewer poisoned birds were produced. These studies cannot thus be compared.
The statement that brodifacoum exhibits much more secondary toxicity risk to birds than other anticoagulants, while not adequately determined, is followed by a statement that difethialone secondary risks are likely comparable to those posed by brodifacoum (page i).

EFED response: This is not an errors response. Policy and procedural matters will be addressed along with other responses after the public-comment period.

Comments on sublethal effects of anticoagulants are speculative and contrary to all research findings from over 20 years of intensive study of these compounds by researchers (pages 74, 96 and elsewhere). The only effect of these products is on the clotting ability of the blood. Similar products are utilized as human medications to prevent blood clots and behavioral side-effects are not noted.

EFED response: Syngenta has provided no supporting documentation for this assertion. The issue of sublethal effects will be addressed through a data call-in.

Likewise, the argument for individual susceptibility is speculative (page 45). Scientific procedures establish median values (such LD or LC values) on which to base regulatory and developmental decisions. Regulatory law cannot be developed based upon an undemonstrated fear of outlying values.

Why is persistence equated with toxicity (pages 60, 61, 66 and elsewhere)? The livers of birds and mammals are designed to sequester and breakdown foreign substances so that they can be excreted from the body. Only circulating levels of anticoagulants in blood that are high enough to affect coagulation are of concern. Low levels of anticoagulant in the liver are biomarkers of some prior exposure but cannot be demonstrated to be causative in deleterious behavioral or health effects.

EFED response: While the retention time is not a direct measure of effect for secondary risk to birds and mammals, it is an important contributing factor. The combination of mean % mortality from secondary laboratory toxicity studies which characterizes the secondary toxicity from short-term exposures, and available data on retention time in both blood and liver which indicates how long toxic levels can persist in target animal tissues, can characterize the secondary risk to birds and mammals. The relationship

between liver residues and toxicity is discussed in the document. Methods to determine what liver concentration might corroborate death from anticoagulant exposure, or even if such a cause-effect relationship is appropriate, e.g., the "threshold of toxicity" concentration in liver tissue are requested in the section on *Uncertainty and Data Needs* in the comparative risk assessment.

Because of the commensal rodent use pattern, it is generally recognized that dogs are the non-target animals most at risk, and certainly more dog incident and treatment data is available than, for example, with birds. Syngenta believes the Agency could have made more use of companion animal hazard and risk information in ranking rodenticides or for application to determinations for other animals. However, dog toxicity information (pages 56-60) is poorly presented in the Agency review document.

An adequate review of the published literature has not been carried out by the Agency and a table of accurate dog LD50 values for rodenticides is not presented, only a commentary citing a mixture of tolerated dose studies of limited utility. Difethialone has a published LD50 value of 4.0 mg/kg (Liphatech Tech Bulletin). Bromadiolone has an LD50 to dogs of 8.1 as reported in Poche (1988). This data supercedes that in Marsh, 1985 as quoted by the Agency. We note that only the lower LD50 values in Marsh, 1985 were chosen for the Agency's example, rather than the middle or upper values within the range of published LD50s that Marsh cites.

The definitive brodifacoum dog study was published by Godfrey, M.E.R., Reid, T.C., and McAllum, H.J.F. (1981). The Acute Toxicity of the Anticoagulant Brodifacoum to Dogs". N.Z. Journal of Experimental Agriculture. 9, 147-149. This article notes a 3.56 mg/kg value based on a test involving 59 adult mixed-breed dogs. The dose that resulted in no adult mortalities was 0.5 mg/kg (59 dogs). Brodifacoum, while highly toxic to rodents, may not possess a significantly greater toxicity to mammals such as dogs than other advanced anticoagulants. The following table derived from the 1990 National Animal Poison Control Center Annual Report supports the contention that non-target poisonings seen with brodifacoum result in no greater percentage of symptoms or death than other commonly-available anticoagulant and non-anticoagulant rodenticides.

Table 2. Call Incidence from National Animal Poison Control Center, 1990*

Rodenticide	% Dog	% Cat	% Symptoms**	% Deaths**
Brodifacoum	81.3	5.9	15.1	6.0
Bromadiolone	78.1	5.3	26.8	9.8
Diphacinone	80.3	2.6	36.8	7.0
Warfarin	79.1	6.7	12.7	13.2
Bromethalin	74.9	9.1	22.9	2.5
Cholecalciferol	81.5	6.5	40.8	12.4

* Percent incidence calculated from total number of calls for each compound
** Totals for combined dog and cat calls

EFED response: EFED believes that the toxicity data presented for the nine rodenticides is comprehensive. Data having more recent dates do not 'supercede' older data; they are simply additional data to consider. As Syngenta knows, EFED assesses risks to nontarget wildlife, not pets. The Agency considers dogs to be domestic pets, and risks to domestic pets are addressed by the Agency's Health Effects Division. Moreover, the Godfrey et al. (1981) study was an antidote study, not an acute-oral toxicity study.